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#### PATENT COOPERATION TREATY

### **PCT**

#### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference X-16280.	FOR FURTHER ACTION	See item 4 below		
International application No. PCT/US2004/037200	International filing date (day/month/year) 01 December 2004 (01.12.2004)	Priority date (day/month/year) 10 December 2003 (10.12.2003)		
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237				
Applicant ELI LILLY AND COMPANY				

1.	This international preliminary report on pa International Searching Authority under R	ntability (Chapter I) is issued by the International Bureau on behalf of the e 44 bis.1(a).		
2.	This REPORT consists of a total of 7 shee	including this cover sheet.		
	In the attached sheets, any reference to the to the international preliminary report on p	ritten opinion of the International Searching Authority should be read as a reference entability (Chapter I) instead.		
3.	This report contains indications relating to	ne following items:		
	Box No. I Basis of	the report		
	Box No. II Priorit			
	Box No. III Non-ee applica	blishment of opinion with regard to novelty, inventive step and industrial lity		
	Box No. IV Lack of	unity of invention		
	Box No. V Reason applica	d statement under Article 35(2) with regard to novelty, inventive step or industrial ility; citations and explanations supporting such statement		
	Box No. VI Certain	documents cited		
	Box No. VII Certain	defects in the international application		
	Box No. VIII Certain	observations on the international application		
4.	4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 bit not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the prior date (Rule 44bis .2).			
Date of issuance of this report 12 June 2006 (12.06.2006)				
	The International Bureau of WI 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Beate Giffo-Schmitt		
Facsi	imile No. +41 22 740 14 35	Telephone No. +41 22 338 87 20		

Form PCT/IB/373 (January 2004)

### **PCT**

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference X-16280.	FOR FURTHER ACTION	See item 4 below		
	International filing date (day/month/year) 01 December 2004 (01.12.2004)	Priority date (day/month/year) 10 December 2003 (10.12.2003)		
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Applicant ELI LILLY AND COMPANY				

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2.	This REPORT consists of a tot	al of 7 sheets, including this cover sheet.
	In the attached sheets, any refe to the international preliminary	rence to the written opinion of the International Searching Authority should be read as a reference report on patentability (Chapter I) instead.
3.	This report contains indication	s relating to the following items:
	Box No. I	Basis of the report
	Box No. II	Priority
	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
	Box No. IV	Lack of unity of invention
	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
	Box No. VI	Certain documents cited
	Box No. VII	Certain defects in the international application
	Box No. VIII	Certain observations on the international application
4.	The International Bureau will not, except where the applicand date (Rule 44bis .2).	communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but it makes an express request under Article 23(2), before the expiration of 30 months from the priority
		Date of issuance of this report 12 June 2006 (12.06.2006)
		12 Julie 2000 (12.00.2000)

Authorized officer

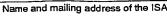
Telephone No. +41 22 338 87 20

Beate Giffo-Schmitt

Facsimile No. +41 22 740 14 35 Form PCT/IB/373 (January 2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

See form PCT/ISA/220  WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHOR (PCT Rule 43 bis.1)  Date of malling (day/month/year) see form PCT/ISA/210 (second sheet)  Applicant's or egent's file reference see form PCT/ISA/220  International application No. PCT/ISA/220  International application No. O1.12.2004  PCT/IS2004/037200  International Patent Classification (IPC) or both national classification and IPC C12N15/12, C07K14/50, A61K38/18, C12N1/19  Applicant ELI LILLY AND COMPANY  1. This opinion contains indications relating to the following items:  Box No. I Basis of the opinion  Box No. II Priority  Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability			
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See form PCT/ISA/220   See paragraph 2 below			
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written opinion of the International Preliminary Examining Authority (PEA) intowers, this association of the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.  If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to			
submit to the IPEA a written reply together, where appropriate, with amounts from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.  For further options, see Form PCT/ISA/220.			
3. For further details, see notes to Form PCT/ISA/220.			
Authorized Officer			



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European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016

Le Cornec, N

Telephone No. +31 70 340-2688



	Box No	
1.	With re	gard to the <b>language</b> , this opinion has been established on the basis of the international application in guage in which it was filed, unless otherwise indicated under this item.
	laı	is opinion has been established on the basis of a translation from the original language into the following iguage , which is the language of a translation furnished for the purposes of international search inder Rules 12.3 and 23.1(b)).
2.	With reneces	egard to any <b>nucleotide and/or amino acid sequence</b> disclosed in the international application and early to the claimed invention, this opinion has been established on the basis of:
	a. type	of material:
	$\boxtimes$	a sequence listing
		table(s) related to the sequence listing
	b. form	nat of material:
		in written format
	⊠	in computer readable form
	c. time	e of filing/furnishing:
		contained in the international application as filed.
	×	filed together with the international application in computer readable form.
		furnished subsequently to this Authority for the purposes of search.
3	h	n addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto as been filed or furnished, the required statements that the information in the subsequent or additional opies is identical to that in the application as filed or does not go beyond the application as filed, as ppropriate, were furnished.
4	. Addit	ional comments:

app!	icability		ion with regard to novelty, inventive step and industrial		
The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:					
	the entire international applicatio	n,			
$\boxtimes$	claims Nos. (13-14, 26-27 and 3	6-37)	partially		
	because:				
☒	the said international application, or the said claims Nos. 13-14, 26-27 and 36-37 (in relation to ind. applicability) relate to the following subject matter which does not require an international preliminary examination (specify):				
	see separate sheet				
	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):				
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.				
	no international search report has been established for the whole application or for said claims Nos.				
	to a side a suppose lighting does not comply with the standard provided for in Annex				
	the written form		has not been furnished		
			does not comply with the standard		
	the computer readable form		has not been furnished		
	·		does not comply with the standard		
	the tables related to the nucleon not comply with the technical r	otide a equir	and/or amino acid sequence listing, if in computer readable form only, do ements provided for in Annex C-bis of the Administrative Instructions.		
	See separate sheet for further	deta	ils		

International application No. PCT/US2004/037200

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

1-41

No:

o: Claims

Inventive step (IS)

Yes: Claims

Claims

1-41

No:

Industrial applicability (IA)

Yes: Claims

1-12,15-25, 28-35, 38-41

No: Claims

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

PCT/US2004/037200

#### Re Item III

### Non-establishment of opinion with regard to industrial applicability

Claims 13, 14, 26, 27, 36 and 37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 13, 14, 26, 27, 36 and 37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are considered relevant:

- D1: WO 03/011213 A (ELI LILLY AND COMPANY; GLASEBROOK, ANDREW, LAWRENCE; HAMMOND, LISA, JA) 13 February 2003 (2003-02-13)
- D2: WO 01/36640 A (CHIRON CORPORATION KYOTO UNIVERSITY) 25 May 2001 (2001-05-25)
- D3: WO 03/059270 A (ELI LILLY AND COMPANY; HEUER, JOSEF, GEORG; KHARITONENKOV, ALEXEI) 24 July 2003 (2003-07-24)

Novelty and inventive step

The subject-matter of present application is novel. Claims 1-41 meet the requirements of article (33(2) PCT).

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2004/037200

Document D1 is regarded as the closest prior art. D1 defines on page 6 lines 28-32 and on page 9 lines 8-26 the possibility of introducing conservative mutations in the sequence of FGF-21. The difference between D1 and the present application is the provision of FGF-21 muteins at specific positions. The problem to be solved by the present invention may therefore be regarded as the provision of further FGF-21 muteins having a higher stability in pharmaceutical formulation conditions (i.e. in the presence of m-Cresol). Example 6 shows (table 4) some FGF-21 muteins having reduced aggregation (reduced average particulate diameter) and nothing about all the other muteins being claimed. Notwithstanding, an inventive step can be acknowledged for those specific substitutions (example 6) showing a reduced aggregation indicating a higher stability.

Clarity and support by the description

Claims 1,15 and 28 are not clear. They do not meet the requirements of Article 6 PCT. Their wording "...substitution of a charged and/or polar but uncharged amino acid...." is very confusing and could allow e.g GLY 42 to be replaced by CYS (i.e. the substitution of a uncharged polar amino acid with a uncharged polar amino acid) which is a conservative substitution as it is explained in D1 (page 9 lines 7-21). Furthermore most of these claimed muteins have not been disclosed in the description and lack also support (article 6 PCT). The same drafting as in claim 4 or 16 would be a good solution to overcome the above problems of clarity.

#### Re Item VIII

Certain observations on the international application

The expression " a biologically active peptide thereof " (claims 1, 15 and 28) is not acceptable (article 6 PCT) because it is vague and unclear.

### **PCT**

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	Date of issuance of this report 12 June 2006 (12.06.2006)					
	The International Bu		Authorized officer			
	34, chemin des 0 1211 Geneva 20,		Beate Giffo-Schmitt			
Facsi	imile No. +41 22 740 14 35		Telephone No. +41 22 338 87 20			

Form PCT/IB/373 (January 2004)

To:    See form PCT/SA/220   WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)	rom the NTERNATIONAL SEARCHING AUTHO	DRITY		HEC'D U 1 APR 2005
Applicants or agent's file reference see form PCT/SA/220  Applicants or agent's file reference see form PCT/SA/220 (second sheet)  Applicants or agent's file reference see form PCT/SA/220 (second sheet)  FOR FURTHER ACTION See paragraph 2 below  International application No.	То:			PCT
Applicant's or agent's file reference See form PCT/ISA/220  International application No. PCT/US2004/037200  International application (IPC) or both national dissification and IPC C12N15/12, C07K14/50, A61K38/18, C12N1/19  Applicant ELI LILLY AND COMPANY  1. This opinion contains indications relating to the following items:  Box No. I Basis of the opinion Box No. II Priority Box No. IV Lack of unity of invention Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability citations and explanations supporting such statement Box No. VI Certain defects in the international application Box No. VIII Certain observations on the International application Box No. VIII Certain observations on the International application FIRTHER ACTION If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant theorems and authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinion of the IPEA, the applicant is invited to submit to the IPEA as written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220.	see form PCT/ISA/220		INTERNATIO	NAL SEARCHING AUTHORITY
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<ul> <li>☑ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>☐ Box No. IV Lack of unity of Invention</li> <li>☑ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>☐ Box No. VI Certain documents cited</li> <li>☐ Box No. VIII Certain observations on the international application</li> <li>☑ Box No. VIII Certain observations on the international application</li> <li>Z. FURTHER ACTION</li> <li>If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1 bis(b) that written opinions of this international Searching Authority will not be so considered.</li> <li>If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.</li> <li>For further options, see Form PCT/ISA/220.</li> </ul>	☑ Box No. I Basis of the o	pinion		
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement  Box No. VI Certain documents cited  Box No. VII Certain defects in the International application  Box No. VIII Certain observations on the international application  FURTHER ACTION  If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.  If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.  For further options, see Form PCT/ISA/220.			gard to novelty, inver	ntive step and industrial applicability
applicability; citations and explanations supporting such statement  Box No. VI Certain documents cited  Box No. VII Certain defects in the International application  Box No. VIII Certain observations on the International application  FURTHER ACTION  If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.  If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.  For further options, see Form PCT/ISA/220.	☐ Box No. IV Lack of unity	of Invention		
<ul> <li>□ Box No. VII Certain defects in the international application</li> <li>☑ Box No. VIII Certain observations on the international application</li> <li>2. FURTHER ACTION</li> <li>If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the international Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this international Searching Authority will not be so considered.</li> <li>If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.</li> <li>For further options, see Form PCT/ISA/220.</li> </ul>	applicability;	citations and explanation	ois.1(a)(i) with regard ns supporting such s	to novelty, inventive step or industrial tatement
<ul> <li>☑ Box No. VIII Certain observations on the international application</li> <li>2. FURTHER ACTION</li> <li>If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.</li> <li>If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.</li> <li>For further options, see Form PCT/ISA/220.</li> </ul>	<del>-</del>		11 <b>A1</b>	
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written opinion of the International Preliminary Examining Authority (* International Searching Authority (* In	, <del></del>			
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	submit to the IPEA a written re months from the date of mailin			
	For further options, see Form	PCT/ISA/220.		
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Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 Authorized Officer

Le Cornec, N

Telephone No. +31 70 340-2688



	Box No	
1.	the land	gard to the <b>language</b> , this opinion has been established on the basis of the international application in guage in which it was filed, unless otherwise indicated under this item.
	☐ Th	is opinion has been established on the basis of a translation from the original language into the following guage , which is the language of a translation furnished for the purposes of international search ider Rules 12.3 and 23.1(b)).
2.	With re	gard to any <b>nucleotide and/or amino acid sequence</b> disclosed in the international application and ary to the claimed invention, this opinion has been established on the basis of:
	a. type	of material:
	$\boxtimes$	a sequence listing
		table(s) related to the sequence listing
	b. fom	nat of material:
	⋈	in written format
	$\boxtimes$	in computer readable form
	c. time	e of filing/furnishing:
	$\boxtimes$	contained in the international application as filed.
		filed together with the international application in computer readable form.
		furnished subsequently to this Authority for the purposes of search.
;	ŀ	n addition, in the case that more than one version or copy of a sequence listing and/or table relating there as been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
	4. Addit	ional comments:

Box	No. III Non-establishment of icability	opin	ion with regard to novelty, inventive step and industrial		
	The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:				
	the entire international applicatio	n,			
×	claims Nos. (13-14, 26-27 and 36-37) partially				
	because:				
⊠	the said international application, or the said claims Nos. 13-14, 26-27 and 36-37 (in relation to ind. applicability) relate to the following subject matter which does not require an international preliminary examination (specify):				
	see separate sheet				
	unclear that no meaningful opin	ion co			
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.				
	the bear established for the whole application or for said claims Nos.				
	the standard provided for in Annex				
	the written form		has not been furnished		
			does not comply with the standard		
	the computer readable form		has not been furnished		
	·		does not comply with the standard		
	the tables related to the nucleon not comply with the technical r	otide a equir	and/or amino acid sequence listing, if in computer readable form only, do ements provided for in Annex C-bis of the Administrative Instructions.		
	See separate sheet for further	deta	ils		

International application No. PCT/US2004/037200

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

1-41

No: Claims

Inventive step (IS)

Yes: Claims

1-41

No: Claims

Industrial applicability (IA)

Yes: Claims

1-12,15-25, 28-35, 38-41

No: Claims

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

#### WRITTEN OPINION OF THE INTERNATIONAL SEARCHING **AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/037200

#### Re Item III

Non-establishment of opinion with regard to industrial applicability

Claims 13, 14, 26, 27, 36 and 37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 13, 14, 26, 27, 36 and 37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are considered relevant:

- D1: WO 03/011213 A (ELI LILLY AND COMPANY; GLASEBROOK, ANDREW, LAWRENCE; HAMMOND, LISA, JA) 13 February 2003 (2003-02-13)
- D2: WO 01/36640 A (CHIRON CORPORATION KYOTO UNIVERSITY) 25 May 2001 (2001-05-25)
- D3: WO 03/059270 A (ELI LILLY AND COMPANY; HEUER, JOSEF, GEORG; KHARITONENKOV, ALEXEI) 24 July 2003 (2003-07-24)

Novelty and inventive step

The subject-matter of present application is novel. Claims 1-41 meet the requirements of article (33(2) PCT).

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2004/037200

Document D1 is regarded as the closest prior art. D1 defines on page 6 lines 28-32 and on page 9 lines 8-26 the possibility of introducing conservative mutations in the sequence of FGF-21. The difference between D1 and the present application is the provision of FGF-21 muteins at specific positions. The problem to be solved by the present invention may therefore be regarded as the provision of further FGF-21 muteins having a higher stability in pharmaceutical formulation conditions (i.e. in the presence of m-Cresol). Example 6 shows (table 4) some FGF-21 muteins having reduced aggregation (reduced average particulate diameter) and nothing about all the other muteins being claimed. Notwithstanding, an inventive step can be acknowledged for those specific substitutions (example 6) showing a reduced aggregation indicating a higher stability.

Clarity and support by the description

Claims 1,15 and 28 are not clear. They do not meet the requirements of Article 6 PCT. Their wording "...substitution of a charged and/or polar but uncharged amino acid...." is very confusing and could allow e.g GLY 42 to be replaced by CYS (i.e. the substitution of a uncharged polar amino acid with a uncharged polar amino acid) which is a conservative substitution as it is explained in D1 (page 9 lines 7-21). Furthermore most of these claimed muteins have not been disclosed in the description and lack also support (article 6 PCT). The same drafting as in claim 4 or 16 would be a good solution to overcome the above problems of clarity.

#### Re Item VIII

Certain observations on the international application

The expression " a biologically active peptide thereof " (claims 1, 15 and 28) is not acceptable (article 6 PCT) because it is vague and unclear.